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SPECIAL ARTICLE

Outbreak of Marburg Hemorrhagic Fever in Angola: A Review of the History of the Disease and its Biological Aspects

B. Lee Ligon, PhD

Transmission of a dangerous infectious disease threatens not merely a local population but the world at large as the result of immigration and increased and faster travel. Any outbreak elicits considerable concern and demands that various precautionary methods be instituted and that the disease be contained as quickly as possible. Recently, an old disease, one that may have been present for centuries and was identified decades ago, reared its ugly head, killing more than 200 people before it was contained. Fortunately, the disease, Marburg hemorrhagic fever, was limited to a small geographic area, but the devastation of lives was much greater than that of many epidemics and was a warning of the numerous factors, including fear, lack of understanding, and deception, that can exacerbate the spread of disease and hinder implementation of restraints. This article reviews the history of the disease caused by Marburg virus and its biological components.
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At a time when the transmission of a dangerous infectious disease threatens not merely a local population but the world at large as the result of immigration and, particularly, increased and faster travel, any outbreak elicits considerable concern and demands that various precautionary methods be instituted and that the disease be contained as quickly as possible. We recently experienced such a situation with the outbreak of a new disease, severe acute respiratory syndrome (SARS), which caused the death of numerous people and raised awareness of the speed with which a disease can reach pandemic proportions. Most recently, an old disease, one that may have been present for centuries and was identified decades ago, reared its ugly head, killing more than 200 people before it was contained. Fortunately, the disease, Marburg hemorrhagic fever (MHF), was limited to a small geographic area, but the devastation of lives was much greater than that of many epidemics and was a warning of the numerous factors, including fear, lack of understanding, and deception, that can exacerbate the spread of disease and hinder implementation of restraints. This article reviews the history of the disease caused by Marburg virus and its biological components.

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History and Recent Outbreaks

Discovery and Early Outbreaks

MHF was described first in 1967, when outbreaks in Germany and the former Yugoslavia were linked to African green monkeys (*Cercopithecus aethiops*) imported from a primate export facility in Entebbe, Uganda.[1] A total of 37 cases, including six from secondary transmission, ultimately were reported; seven deaths occurred in primary cases.[2] In England, an infectious agent, unlike any previously seen, was recovered from the blood and organs of these persons. Researchers called the agent Marburg virus.[3-6]

The first recognized outbreak of Marburg virus in Africa occurred in February 1975 (Fig 1), eliciting considerable press coverage (Fig 2). The index case was a young Australian who had been touring Rhodesia. He was admitted to the Johannesburg Hospital and died on the seventh day from hemorrhage resulting from a combination of disseminated intravascular coagulation and hepatic failure. Tests performed by the Centers for Disease Control and Prevention (CDC) confirmed that he had contracted Marburg virus (Fig 3). Two secondary cases, the first patient's traveling companion and a nurse, also were reported. Both of these patients survived after being given vigorous supportive treatment and prophylactic heparin.[7]

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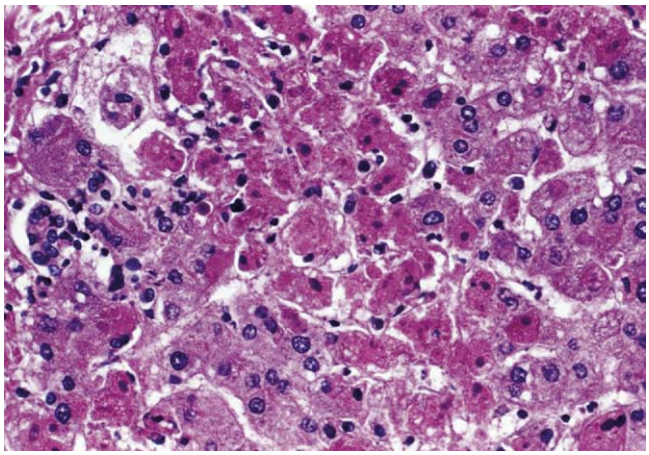

Figure 1 Photomicrograph reveals the cytoarchitectural histopathologic changes that were detected in a liver sample from a Marburg patient (case 1) who was treated in Johannesburg, South Africa in 1975. (Public domain; available through the CDC.) (Color version of figure is available online.)

Figure 2 Articles published during the 1975 Marburg outbreak in southern Africa demonstrate the extent of press coverage, which was constant and not always accurate. (Provided by Dr. J. Lyle Conrad; public domain, available through the CDC.)

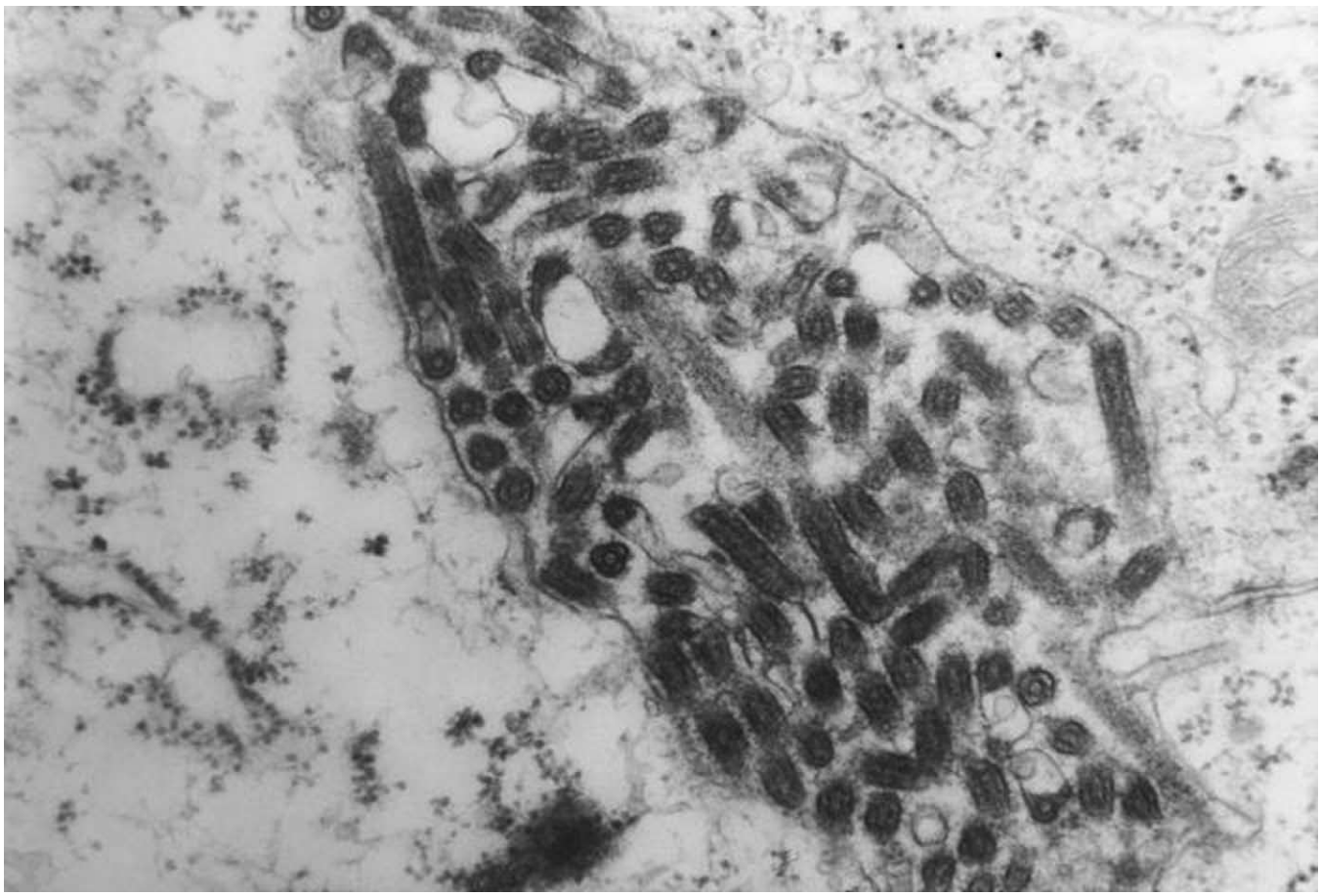

Figure 3 Transmission electron micrograph, photographed at the CDC, Atlanta, Georgia, which confirmed the suspicion that the 1975 hemorrhagic fever patient had acquired the Marburg virus while traveling through Rhodesia. Note that the cylindrical Marburg virions were sectioned in various planes, explaining why some are seen as longitidunal sections, whereas others are seen cut in a transaxial plane and look circular. (Photograph provided by Dr. J. Lyle Conrad; public domain, available through the CDC.)

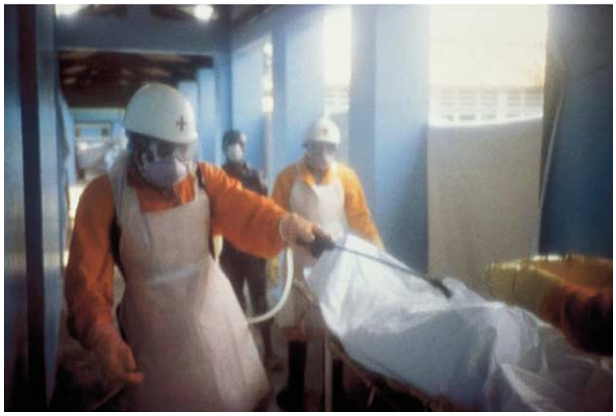

Figure 4 A local Red Cross team is disinfecting a body bag of a victim of the Ebola outbreak in Kikwit, Democratic Republic of the Congo, 1995. (Provided by Ethleen Lloyd; public domain, available through the CDC.) (Color version of figure is available online.)

In 1980, two other cases occurred, one of which was in Western Kenya not far from the Ugandan source of the monkeys implicated in the 1967 outbreak. The patient's attending physician in Nairobi became the second case. Yet another infection was diagnosed in 1987 when a young man who had traveled extensively in Kenya became ill and died.[6]

In 1995, a related disease, Ebola hemorrhagic fever (EHF), reemerged in Kikwit, Democratic Republic of the Congo. The disease was contained by the implementation of house-to-house searches, interviews of healthcare personnel, retrospective contact tracing, and direct follow-up of suspect cases, as well as other measures (Fig 4). The onset of the earliest documented case occurred on January 6, 1995, and the last patient died on July 16, 1995. During that period, a total of 315 cases of EHF were reported, including 80 cases among healthcare workers, with an 81 percent case fatality rate. Two individuals were reported to be the source of infection in more than 50 cases, highlighting the potential for fast and widespread transmission of diseases.[8]

Three years later, an outbreak of MHF occurred in 1998 in northeastern Democratic Republic of the Congo; it was the largest outbreak to have occurred at that time.[9,10] The epicenter of the outbreak was the village of Durba in the Haut-Uélé District, Oriental Province. Because of the remoteness of the area and the fact that a civil war that was occurring, access to the area and evaluation of the disease were delayed until May 1999, when an international team of investigators was able to perform studies. These investigators identified 73 cases (8 laboratory-confirmed and 65 suspected and later identified retrospectively).[11] Later follow-up surveillance identified more than 150 cases through December 2000.[12]

2005 Outbreak in Angola

On March 22, 2005, the BBC news service reported that at least 96 people had died in the previous 5 months in Angola from an outbreak of a disease reported to have symptoms similar to those of Ebola and thought to be Marburg disease. The news service also reported that Vice Health Minister Jose Van Dunem had said that 101 cases of the illness had been reported in a hospital in the city of Uife, that 93 people had died, and that two people had left the hospital without having been properly discharged.[13]

On March 23, 2005, the World Health Organization (WHO) confirmed that Marburg virus was the causative agent of the outbreak of viral hemorrhagic fever in Uige Province in northern Angola. On March 25, 2005, the CDC reported that their Special Pathogens Branch had identified the presence of Marburg virus in 9 of 12 specimens from patients who had died during the outbreak in Angola. The CDC Branch is a WHO Collaborating Center on Viral Hemorrhagic Fevers. Testing done in that laboratory had confirmed the presence of the virus using a combination of reverse transcriptase polymerase chain reaction (PCR), antigen-detection enzyme-linked immunosorbent assays (ELISAs), and virus isolation. The CDC immediately posted an outbreak notice on their travelers' health website.

On that same day (March 25), the BBC news service reported that the virus had reached the capital, Luanda, where six victims, all of whom had visited Uige recently, had been diagnosed. The news service also reported that the European Union had announced that it would donate $650,000 US.[14]

Between October 1, 2004, and March 29, 2005, a total of 124 cases were identified, of which 117 were fatal. All of the cases had originated in Uige Province. Approximately 75 percent of the reported cases had occurred in children aged 5 years or younger.[15,16]

By April 6, 156 people were reported dead, and working conditions were extremely difficult for healthcare providers, who were facing a huge challenge. Swathed in head-to-toe protective medical gear that requires half an hour to put on and 45 minutes to remove, physicians were contending with extreme heat as well as a feeling of helplessness, knowing that there is no cure for the disease.[17]

Exacerbated by fear and ignorance among the people, who feared going to the hospital because they considered it the source of the disease, the death toll continued to climb. News reports told of a crisis situation in which some Angolans were taking out their anxiety on healthcare providers, requiring mobile surveillance teams in Uige to suspend operations when vehicles were attacked and damaged by residents. On April 8, the news media reported that the organization staff in Uige was notified of several workers' deaths but that teams were unable to investigate the causes of death or collect the bodies for burial. One report said that residents who erroneously thought the workers were exposing them to the virus had killed them. A spokesperson for WHO was reported to have explained that "the dramatic symptoms of Marburg hemorrhagic fever and its frequent fatality are resulting in a high level of fear, which is further aggravated by a lack of public understanding about the disease. Moreover, because the disease has no cure, hospitalization is not associated with a favorable outcome, and confidence in the medical care system has been eroded."[17,18]

Days later, news reports were providing details of the results of fear and ignorance that were fueling the outbreak, including that terrified residents had stoned WHO worker's vehicles and that they were hiding patients at home, contributing to the spread of the disease. Fatomata Diallo, a WHO country repre-

Figure 5 The body of a victim of Marburg hemmorhagic virus is being removed by medical personnel wearing protective gear. (Color version of figure is available online.)

sentative was quoted as explaining that the fear is seen "especially in this kind of epidemic where you have to have special clothes, like an astronaut, and come into the family to take a sick person or suspected case (Fig 5). When you come to take away a body, a dead body, with all this kind of clothing, sometimes it is not easy for the community to accept it."[19]

On Friday, April 8, WHO issued through the United Nations an appeal for $2.4 million US to support the emergency response to the outbreak. WHO already had established an international network of laboratories, including two portable field laboratories in Angola, to help in the investigation of Marburg and other viral hemorrhagic fevers

On April 22, 2005, a report was issued stating that the outbreak of the virus that had claimed 244 lives in Angola had been confined to the province of Uige, as no new cases had been detected outside the northern region. Deputy Health Minister Jose Van Dunem was quoted as saying that they had "circumscribed the epidemic to the province of Uige" and that four provinces and the capital Luanda had not reported any new cases. Of the 244 persons who had died (of a total of 266 cases), 228 were from the northern province of Uige. He also was quoted as saying that "the disease is on a decline" and that "the epidemic is under control because we know how it is transmitted, how to break the chain of transmission."[20]

Update: As of 16 June, the Ministry of Health in Angola had reported a total of 422 cases and 356 deaths in Uige Province. Twenty-one contacts were being followed in Uige municipality, and 111 were being followed in other municipalities. Alerts to potential cases existing in difficult-to-reach locations outside Uige municipality had been received and plans were underway for a team to travel by helicopter to investigate these cases. http://www.who.int/csr/don/2005_06_17/en/index.html

Clinical Manifestation

The disease presents as an acute febrile illness. It can progress within 6 to 8 days to severe hemorrhagic manifestations. The incubation period of 5 to 10 days is followed by a sudden onset marked by fever, chills, headache, and myalgia. Approximately the fifth day after the onset of the symptoms, a maculopapular rash may manifest, after which the individual may experience nausea, vomiting, chest pain, sore throat, abdominal pain, and/or diarrhea. Patients often develop severe hemorrhagic manifestations between days 5 and 7, and fatal cases usually have some form of bleeding, often from multiple sites. Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multiorgan dysfunction. The fatality rates have ranged from 25 to 80 percent, with higher rates occurring in outbreaks lacking effective case management.[6,15] In the case of the outbreak in Angola, WHO has reported a greater than 90 percent case fatality rate, rendering this outbreak the deadliest on record for this rare disease: the outbreak in the Democratic Republic of Congo from 1998 to 2000 had a case fatality rate of 83 percent.[21]

Etiology

The Marburg virus, the natural reservoir for which remains unknown, causes MHF. Thought to be of zoonotic origin, it is from the same family (*Filoviridae*) as the virus that causes EHF. Both viruses are among the most virulent pathogens known to infect humans, and, although both diseases have been rare occurrences, they have the capacity to cause dramatic outbreaks with high fatality rates.[22] Except for the Ebola virus subtype Reston, all members of the *Filoviridae* are thought to be African viruses.

The viruses have similar morphologies: long filamentous particles often have bizarre configurations and may be as long a 14,000 nm. They are 80 nm in width and contain a single negative-sense genome that codes for seven polypeptides (Fig 6). Peters and coworkers have published a review of the molecular organization and replication strategy of this virus group and comparison with other closely related families.[23]

The viruses are largely destroyed by heat and acidity, but they may persist for weeks at room temperature. The surface glycoprotein self-associates to form the virion surface spikes and has high sugar content that may contribute to its low capacity to elicit neutralizing antibodies.[24]

Epidemiology

Because the origin of every index case of human filovirus disease is unknown, outbreaks thus far have been based on person-to-person transmission, which is fueled by the high and persistent viremia that makes the syndrome and by the presence of virus in other body fluids. In the original Marburg outbreak, sources were tissues of monkeys used to prepare cell cultures for manufacture of poliovirus vaccine; secondary infection was limited primarily to medical workers who failed to take appropriate precautions to prevent direct contact of skin with body fluids.[4] Although available evidence suggests a nonprimate reservoir for the virus, intensive search has failed to elucidate what it might be.[24] Epidemiologic studies have yielded no evidence for an important role of airborne particles in either Ebola or Marburg disease, al-

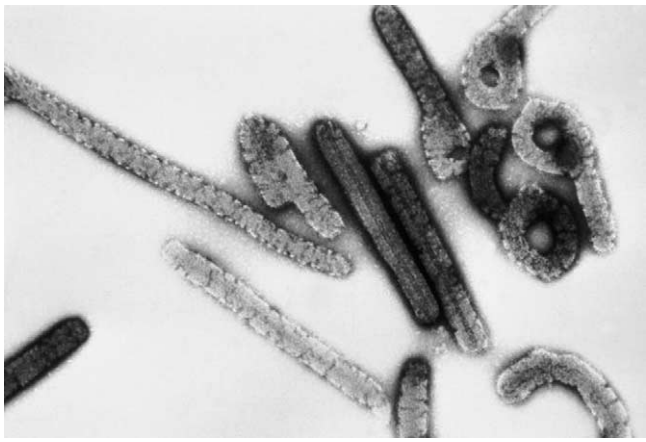

Figure 6 Negative stained transmission electron micrograph depicts numerous filamentous Marburg virions, which had been cultured on Vero cell cultures and purified on sucrose, rate-zonal gradients. Note the virus' morphologic appearance with its characteristic "Shepherd's Crook" shape. Magnification ×100,000. (Photograph provided by Drs. Erskine Palmer and Russell Regnery; public domain, available through the CDC.)

though formal laboratory assessments show a high degree of aerosol infectivity for monkeys.

Pathology and Pathogenesis

Marburg virus replicates well in virtually all cell types, including endothelial cells, macrophages, and parenchyma cells of multiple organs, in both humans and animal models. In vivo and in vitro viral replication is associated with cellular necrosis. Significant findings at the light-microscopic level include liver necrosis with Councilman bodies, interstitial pneumonitis, cerebral glial nodules, and small infarcts. Antigen and virions are found in abundance in fibroblasts, interstitium, and the appendages of the subcutaneous tissues in fatal cases. They may escape through small breaks in the skin or possibly through sweat glands, in which case they may be correlated with the established epidemiologic risk of close contact with patients and the touching of the deceased. Inflammatory cells are not prominent.[24]

Transmission

Primary transmission of the virus from the natural reservoir appears to occur only in sub-Saharan Africa. Secondary person-to-person transmission occurs in both community and nosocomial settings. Bausch and associates[12] conducted two antibody surveys to assess risk factors for MHF in the Democratic Republic of the Congo, where confirmed transmission had occurred. Although the number of antibody-positive survey participants was small, these investigators were able to systematically identify and quantify several risk factors. The local mines were found to be a probable site of primary infection with the virus, most likely through exposure to the primary zoonotic reservoir; this conclusion was based on the preponderance of antibody in male miners without obvious evidence of person-to-person transmission, as well as other factors. Close contact with case patients with the disease or corpses was identified as a risk factor for secondary transmission of Marburg virus. Another possible risk factor was having received an injection in the past year, but the actual association was not clear.

Unprotected exposure to dead bodies is a significant cause of further spread. Hence, in the outbreak in Angola, mobile teams, dressed in their protective gear, prepared, transported, and buried the bodies of individuals who were fatal victims of the disease (Fig 7).[25] Cultural practices of burying the dead, despite warnings otherwise, have contributed to the spread of the disease. Aerosol transmission has not been described, but it cannot be eliminated as a possible means of transmission.[5]

Diagnosis

Physicians should consider the diagnosis of MHF among febrile patients who, within 10 days before onset of fever, have traveled in an area where Marburg virus is endemic; have had direct contact with blood, other body fluids, secretions, or excretions of a person or animal suspected of having MHF; or have worked in a laboratory or animal facility that handles hemorrhagic fever viruses.[15]

Diagnosis is established by isolation of virus because antibodies to the agent usually are not present before death or defervescence. An ELISA method correlates well with viral presence in blood, and PCR has proved to be successful.

As with EHF, MHF must be differentiated from other viral hemorrhagic diseases in Africa, a well as from many bacterial, rickettsial, and protozoal diseases that may have similar presentations early in the clinical course. Yellow fever and Rift Valley fever can be eliminated by the absence of jaundice. For patients outside Africa, a travel history is a primary diagnostic tool.

Treatment and Prevention

No vaccine or curative treatment is available for MHF. Supportive treatment, including balancing the patient's fluids

Figure 7 Physicians and other healthcare providers donned head-to-toe protective medical gear for treating patients and conducting searches. (Color version of figure is available online.)

and electrolytes, maintaining the oxygen status and blood pressure, replacing lost blood and clotting factors, and treating them for any complicating infections, should be provided. Treatment also has included transfusion of fresh-frozen plasma and other preparations to replace the blood proteins important in clotting. A controversial treatment is the use of heparin to prevent the consumption of clotting factors because some researchers argue that the consumption is part of the disease process. Because of the means of transmission, hospital practices should include implementing contact and droplet precautions, in addition to wearing eye protection or a face shield.[6,15]

Public Health Measures

Numerous public health measures were initiated during the outbreak in Angola. WHO and international partners in the Global Outbreak Alert and Response Network (GOARN) worked with the Ministry of Health in Angola to conduct an investigation and public health response to the outbreak. Outbreak-control efforts were directed at providing technical support for case management, strengthening infection control in hospitals, improving surveillance and contact tracing, and educating residents about the disease and its mode or transmission. As part of a public health response, in addition to posting information for travelers, the CDC sent personnel to join the WHO-coordinated GOARN response team. The CDC representatives assisted with epidemiologic investigation, infection control, and laboratory diagnosis. The CDC also provided laboratory and other scientific and logistical support.[15]

In most Western countries, MHF is a reportable or notifiable disease. Cases or outbreaks also should be reported to the WHO. The virus is a hazard category 4 virus and should be handled in a containment level 4 laboratory. Strict isolation and barrier nursing are recommended, and the handling of biological specimens for diagnosis and patient management should be performed according to regulations governing risk assessment and control. Case contacts or individuals with exposure in laboratories should be placed under health surveillance for 21 days after their last exposure to infection. If they should become feverish, they should undergo risk assessment and perhaps be admitted to strict isolation pending the results of diagnostic tests.[5]

In conjunction with the WHO, the CDC has developed guidelines entitled "Infection Control for Viral Hemorrhagic Fevers in the African Health Care Setting." English and French versions of the manual can be obtained online at http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual.htm.

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